REMARKS

The present invention relates to compositions and methods to modulate one or more of the contractility and angiogenic activity of a mammalian muscle or endothelial cell or tisssue. Claims 1-55 are pending in the present application. Claims 3-4, 10, 13, 19-21, 23, 27 and 29-53 have been withdrawn from consideration without prejudice to the inclusion of the subject matter contained therein in any later filed divisional or continuation applications. Claims 1-2, 5, 7, 8, 11, 15-16, 18, 22, 24-25, 28 and 54 have been amended and claims 9, 12, 14, 15, 16 and 17 have been canceled herein. Support for the amendment to claim 46 and the is discussed in more detail below.

Information Disclosure Statement (IDS)

Applicants acknowledge the Examiner's receipt and consideration of the references listed in the IDS filed on July 31, 2003 and April 15, 2002.

Objection to Oath

The Examiner has objected to the Oath or Declaration filed in the present application. Specifically, the Examiner has stated that the Oath or Declaration is defective because the signature of co-inventor Abd Al-Roof Higazi is unclearly set forth and the Examiner requires a new Oath or Declaration identifying the present application by application and filing date.

Applicants respectfully submit that the signature of Dr. Abd Al-Roof Higazi as set forth on the Declaration and Power of Attorney is clearly legible and is not therefore "unclearly set forth". Further, it is completely within an Applicant's purview to place a signature on a Declaration and Power or Attorney in the manner in which the Applicant is accustomed to affixing his signature to any other document. The signature set forth on the Declaration and Power of Attorney filed on January 9, 2002 is the signature of Dr. Abd Al-Roof Higazi, and it is clearly legible, and therefore not "unclearly set forth". For these reasons, Applicants respectfully request reconsideration and withdrawal of the Examiner's objection to the Oath or Declaration.

Objections to the Specification and Claim 9

The Examiner has objected to the specification, specifically the term "PCR" at page 15, line 27, the term "SDS-PAGE" at page 67, lines 12-13 and the term "MALDI-TOF" at page 68, line 17, and has indicated that the above abbreviations should be spelled out in full at the first instance of use. Applicants have submitted herewith amended replacement paragraphs for the paragraphs containing the above abbreviations. Applicants submit that the amended replacement paragraphs add no new matter, but rather merely spell out abbreviations used in the specification as filed.

The Examiner has objected to the phrase "calculated from the ratio of the kinetic constants (Kd =kd/ka)" and has indicated that the phrase should be changed to "calculated from the ratio of the association constant to the disassociation rate constant" and further indicates the equation should be K_a/K_b.

It is settled that the "patent law allows the inventor to be his own lexicographer." *Chicago Steel Foundry Co. v. Burnside Steel Foundry Co.*, 132 F.2d 812 (7th Cir. 1943). Applicants have defined an equilibrium dissociation constant (Kd) as set forth in the specification as filed, and have provided an equation to calculate such a rate dissociation constant. The calculation provided is not repugnant to the definition of a dissociation rate constant, and as such, Applicants' definition is sufficient. Moreover, Applicants provide the results of the calculations (Table 1, page 73) using the equation set forth in the specification as filed in order to determine the value of Kd. One of skill in the art, armed with a calculator, would readily realize that Applicants' equation is not repugnant to determining the value of an equilibrium dissociation constant (Kd), and that Kd = kd/ka). Further, the Examiner suggests that Applicants should introduce into the specification a rate constant (K_b) that is not supported in the specification and would thus constitute new matter. 35 U.S.C. §132 prohibits Applicants from introducing new matter in the specification, and thus if Applicants were to comply with the Examiner's suggestion, Applicants would be in violation of U.S. Patent Law. Therefore, Applicants respectfully urge the Examiner to withdraw the present rejection to the specification.

The Examiner has also objected to claim 9 and has required Applicants to amend the phrase "two chain urokinase" to read "two-chain urokinase". Applicants have canceled claim 9 herein.

Rejection of Claims 1-2, 6-9, 11-12, 14-18, 22, 24-26, 28 and 54-55 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 1-2, 6-9, 11-12, 14-18, 22, 24-26, 28 and 54-55 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner contends that the term "modulate" and the phrase "modulate one or more of the contractility and the angiogenic activity" in claims 1 and 28 is unclear as to whether it encompasses up-regulation or down-regulation and is also unclear as to the biological activities regulated. Further, the Examiner opines that claims 1 and 2 are unclear in that "one or more of the contractility and the angiogenic activity" does not specify which biological activities are modulated by uPA kringle.

Applicants, while not necessarily in agreement with the Examiner, but rather in a good faith effort to expedite the prosecution of the present application, have amended claim 1 to recite "increase the contractility". Support for the present amendment can be found throughout the specification as filed, specifically at, for example, page 17, beginning at line 4, page 20, beginning at line 7, page 56, beginning at line 23 and page 60, beginning at line 18.

The Examiner has rejected claims 1, 9, 22 and 24-25 and the claims that depend therefrom for being indefinite. In particular, the Examiner opines that the term "at least about 75%" is indefinite because "at least" is narrower than "about" which falls outside of the range set by "at least". Applicants, while not wishing to acquiesce to the Examiner's reasoning, but rather in a good faith effort to expedite the prosecution of the present application, have amended claims 1, 9, 11, 22, 24 and 25 to delete the term "at least about 75%". Applicants respectfully assert that amended claims 1, 9, 11, 22, 24 and 25 are not indefinite.

The Examiner has rejected claim 2 as being unclear as to whether the composition covalently or non-covalently comprises the growth factor domain, the connecting peptide and/or the protease domain. Applicants, while not necessarily agreeing with the Examiner's reasoning, but rather in a good faith effort to expedite the prosecution of the present application, have amended claim 2 to recite a connecting peptide, as set forth in the Response to Restriction Requirement. Applicants submit that claim 2, as amended, is not indefinite because it clearly sets forth a composition comprising the connecting peptide.

The Examiner has rejected claim 28 because, in the Examiner's opinion, the term "one or more polypeptides" is indefinite because only one polypeptide was elected in Response

to the Restriction Requirement. Applicants submit that the as amended claim 28 is no longer indefinite because it clearly refers to SEQ ID NO:8 which Applicants elected in the Response to Restriction Requirement.

The Examiner has rejected claims 12 and 14 as being, in the Examiner's opinion, vague as to whether the kringle fragment or ATF fragment comprise heterogeneous components because the claims do not set forth sequence identifiers, and could permit numerous possibilities as to the identity of the kringle and ATF fragments. Applicants, while not necessarily agreeing with the Examiner's reasoning, but rather in a good faith effort to expedite the prosecution of the present application, have canceled claims 12 and 14 and incorporated the subject matter therein into the claims from which they depend, namely claims 1 and 11, respectively. Claim 1 and 11, as amended, recited sequence identifiers which are fully supported in the specification, figures and sequence listing as filed, and thus leave no doubt as to the identity of isolated kringle and isolated ATF.

The Examiner has rejected claim 15, specifically because the Examiner views disinhibiting as not being equal to enhancing the contractility, and the Examiner questions whether the claim is directed to an enhancing or disinhibiting process. Applicants, as stated above, are permitted to act as their own lexicographer. However, while not wishing to acquiesce to the Examiner's reasoning, but rather in a good faith effort to expedite the prosecution of the present application, Applicants have amended claim 15 to recite "increasing". The term "enhance or disinhibit" is defined in the specification as filed, specifically at page 17 beginning at line 3, as is the term "enhance or disinhibit the contractility", which means to increase the contractility. Thus, the present amendment is fully supported in the specification as filed and the instant amendment includes no new matter.

The Examiner has rejected claim 22, specifically the term "scuPA$^{\Delta 136\text{-}143}$" because, in the Examiner's opinion, the term is insufficiently defined in the specification and could be interpreted as a scuPA with a deletion only at amino acid residue 136. Applicants respectfully argue that if there was only a deletion at amino acid 136, the claim would recite "scuPA$^{\Delta 136}$", and not "scuPA$^{\Delta 136\text{-}143}$". If the Examiner's interpretation was correct, "-143" would be superfluous and unnecessary, and would not have been set forth in the present application. Further, the notation employed by Applicants is the standard in the art for designating a deletion of a portion of a molecule, and would not confuse the skilled artisan armed with the present

disclosure. However, while Applicants do not necessarily agree with the Examiner's reasoning, in a good faith effort to expedite the prosecution of the present application, Applicants have amended claim 22 to recite "scuPA$^{(\Delta 136\text{-}143)}$". Applicants submit that the present amendment merely clarifies claim 22 by reciting a polypeptide comprising a deletion from amino acid 136 to 143, as set forth in the specification as filed, specifically at page 66, line 1 and at page 67, beginning at line 15, and thus the present amendment adds no new matter.

The Examiner has rejected claim 54 as being indefinite. Specifically, the Examiner contends that it is not clear what the term "as a symptom thereof" refers to and lacks antecedent basis. Applicants respectfully submit that the word "a" precedes the first use of "symptom" in claim 54, as indicated by the section quoted by the Examiner above. However, Applicants, while not wishing to acquiesce to the Examiner's reasoning, but rather in a good faith effort to expedite the prosecution of the instant application, have amended claim 54. Specifically, Applicants assert that it is clear that symptom refers to a symptom of a disease or condition, and that as before, symptom has sufficient antecedent basis. Further, as indicated in the Response to Restriction Requirement, Applicants have elected uPA kringle from the list of polypeptides set forth in claim 54, and have amended the claim 54 to reflect Applicants' election.

For the reasons set forth above and the amendments set forth in the claim listing, Applicants submit that the Examiner's rejection to claims 1-2, 6-9, 11-12, 14-18, 22, 24-26, 28 and 54-55 pursuant to 35 U.S.C. §112, second paragraph, have been overcome or are now moot. Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejection of Claims 1-2, 5-9, 11-12, 14-18, 22, 24-26, 28 and 54-55 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1-2, 5-9, 11-12, 14-18, 22, 24-26, 28 and 54-55 because, in the Examiner's view, the specification contains subject matter which was not described in such a way as to reasonably convey to one of skill in the art that the inventors had possession of the claimed invention. The Examiner states that Applicants are in possession of an isolated composition comprising the kringle sequence, the amino terminus fragment, the connecting peptide, the protease domain, a uPA variant (scuPA $^{\Delta 136\text{-}143}$), an inducing compound that mediates muscle contraction and a kit comprising the composition. However, the Examiner asserts that Applicants are not in possession of a composition comprising any uPA variants or

derivatives comprising about 75% homology with the polypeptides set forth in claims 1, 9, 11, 22 or 25, a composition comprising an unlimited number of fragments or a kit comprising an unlimited number of fragments.

Applicants, while not necessarily in agreement with the Examiner, but rather in a good faith effort to expedite the prosecution of the present application, have amended claims 1, 9, 11, 22, 24 and 25 to recite what Applicants regard as their invention. The Examiner has stated that Applicants are in possession of the peptides recited in the presently amended claims, and thus, have overcome the Examiner's rejection. Further, as indicated above, Applicants have amended claim 2 and claim 54 to recite a connecting peptide and uPA kringle, respectively, which the Examiner has stated Applicants are in possession of, and similarly, Applicants, in light of the present amendments and the Examiner's own admission, submit that the present rejection should be reconsidered and withdrawn.

The Examiner contends that the specification only provides a working example for modulating muscle contractility with a uPA kringle polypeptide, and that the claimed biological activity of uPA kringle is not supported by the specification. While Applicants do not agree with the Examiner's characterization of the data, in an effort to expedite the prosecution of the present application, Applicants have amended claim 1, 17, 28 and 54 to recite "increase the contractility". The Examiner has stated that Applicants provide a working example of the present invention (page 7, second paragraph of the present Office Action), and thus, by the Examiner's own admission, Applicants were in possession of the present invention.

For the reasons set forth above, Applicants respectfully submit that the rejection to claims 1-2, 5-9, 11-12, 14-18, 22, 24-26, 28 and 54-55 has been overcome or is now moot. Reconsideration and withdrawal of the rejection of these claims pursuant to 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection of Claims 1-2, 5-6, 9, 11, 17-18, 24-26 and 28 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 1-2, 5-6, 9, 11, 17-18, 24-26 and 28 pursuant to 35 U.S.C. §102(b) as being anticipated by Gurewich (U.S. Patent 5,759,542) as evidenced by Li et al. (1992, Biochemistry 31: 9562-9571).

It is hornbook law that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art

reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). That is not the case here. The Examiner argues that SEQ ID NO:18, residues 48-135 as taught by Gurewich is 100% identical to SEQ ID NO:1 as set forth in claim 1 of the present application. Applicants submit that Gurewich does not anticipate the as amended claim 1 because Gurewich does not teach the identical invention. Gurewich teaches a fusion protein consisting of "at least amino acids 1 to 132" of SEQ ID NO:18. Firstly, Gurewich teaches a fusion protein in which a drug is bound to residues 1-132, and secondly, residues 1-132 are not the same as residues 1-88, and therefore, Gurewich does not teach the identical invention set forth in the as amended claim 1, and therefore does not anticipate the present invention.

The Examiner also argues that SEQ ID NO:18, residues 136-411 as taught by Gurewich is 100% identical to SEQ ID NO:5 as set forth in claim 5 of the present application (the Examiner stated SEQ ID NO:1, but Applicants presume that the Examiner intended to write SEQ ID NO:5, as it is the only sequence listed in claim 5). Applicants submit that Gurewich does not anticipate the as amended claim 5 because Gurewich does not teach the identical invention. Gurewich teaches a fusion protein consisting of "at least amino acids 1 to 132" of SEQ ID NO:18. Firstly, Gurewich teaches a fusion protein consisting of at least residues 1-132 and a drug, and further, if Gurewich teaches a composition that consists of at least residues 1-132 and claim 5 as amended claims a composition comprising a polypeptide wherein the polypeptide consists of a polypeptide having the amino acid sequence beginning at residue 136, Gurewich necessarily fails to anticipate the present invention.

The Examiner has rejected claim 17 and 18 because, in the Examiner's view, Gurewich teaches a fusion protein wherein a uPA polypeptide is linked to a drug and has the ability to inhibit biological function or angiogenic activity of smooth muscle cells or vascular smooth cells. Claim 17 depends from claim 1, which recites a composition comprising a polypeptide wherein the polypeptide consists of a polypeptide having the amino acid sequence of SEQ ID NO:1. Thus, the polypeptide set forth in claim 1, from which claim 17 depends, does is not a fusion protein, and as such, is not the identical invention and is not anticipated by Gurewich. Claim 18, which depends from claim 2, which depends from claim 1, recites a

comprising a polypeptide wherein the polypeptide consists of a polypeptide having the amino acid sequence of SEQ ID NO:1 and further comprises the uPA connecting peptide. As set forth above, SEQ ID NO:1 is not identical to a fusion protein consisting of at least residues 1-132 or SEQ ID NO:18 as set forth in Gurewich, and a composition further comprising the uPA connecting peptide does not result in the identical composition allegedly taught by Gurewich, and therefore, Gurewich cannot anticipate the present invention.

The Examiner has rejected claim 6 as being anticipated by Gurewich because, in the Examiner's view, Gurewich teaches that the fusion protein is administered to a human. Applicants respectfully argue that claim 6 is not limited to a human, but rather recites a mammal, and therefore, Gurewich does not teach the identical invention. Further, as set forth above, Gurewich teaches a fusion protein that is not identical to the compositions presently recited in claim 1, from which claim 6 depends, and therefore, Gurewich does not anticipate the present invention.

The Examiner has rejected claim 2 as being anticipated by Gurewich because, in the Examiner's view, Gurewich teaches that the uPA polypeptide of SEQ ID NO:18 comprises a growth factor domain. Applicants note that claim 2 as amended claims a connecting peptide, which is not taught by Gurewich, and thus, Gurewich does not anticipate the present invention.

The Examiner has rejected claim 9 as being anticipated by Gurewich because, in the Examiner's view, Gurewich teaches multiple chains of uPA which are 100% identical to SEQ ID NO:3 in the present application. The Examiner further cites Li et al. as evidence that the high molecular weight uPA is the two chain form of uPA. Applicants respectfully submit that the Examiner's rejection of claim 9 is not moot in light of Applicants cancellation of claim 9.

The Examiner has rejected claim 11 as being anticipated by Gurewich. Specifically, in the Examiner's view, Gurewich teaches a composition comprising the amino terminal fragment (ATF) of uPA (residues 1-135 of SEQ ID NO:18), which is 100% identical to SEQ ID NO:4 set forth in the instant claim 11. Applicants submit that Gurewich does not anticipate the presently amended claim 11 because SEQ ID NO:4 is 135 amino acids in length and Gurewich teaches a fusion protein that is 132 amino acids in length and is fused to a drug. Therefore, Gurewich does not teach the identical invention as set forth in the amended claim 11, and cannot therefore anticipate the present invention.

The Examiner has rejected claim 24 and 28 as being anticipated by Gurewich.

Specifically, in the Examiner's opinion, residues 1-143 of SEQ ID NO:18 of Gurewich is 100% identical to SEQ ID NO:8 of the present application. Applicants respectfully submit that Gurewich does not teach polypeptide that consists of a polypeptide having the amino acid sequence corresponding to SEQ ID NO:8, as set forth in the as amended claims 24 and 28, but rather teaches a fusion drug consisting of uPA amino acids 1-132 fused to a drug. This is not the identical invention, and as such, cannot anticipate the present invention.

The Examiner has rejected claim 25 as being anticipated by Gurewich because, in the Examiner's view, residues 48-143 of SEQ ID NO:18 of Gurewich is 100% identical to SEQ ID NO:9 of the present application (the Examiner stated SEQ ID NO:8, but Applicants presume that the Examiner intended to write SEQ ID NO:9, as it is the only sequence listed in claim 25). Applicants respectfully submit that Gurewich does not teach polypeptide that consists of a polypeptide having the amino acid sequence corresponding to SEQ ID NO:9, as set forth in the as amended claim 25, but rather teaches a fusion drug consisting of uPA amino acids 1-132 fused to a drug. This is not the identical invention, and as such, cannot anticipate the present invention.

The Examiner has rejected claim 26 as being anticipated by Gurewich, specifically, the Examiner is of the opinion that Gurewich teaches that the fusion drug is for therapeutic use and formulated with a pharmaceutically acceptable carrier. Applicants, as set forth above, submit that Gurewich does not teach any of the polypeptides or compositions presently claimed but rather teaches a fusion drug consisting of residues 1-132 of SEQ ID NO:18, and thus, the non-identical fusion drug Gurewich teaches cannot anticipate the present invention.

For the reasons set forth above, Applicants submit that Gurewich fails to anticipate the present claims as amended. Reconsideration and withdrawal of the rejection of claims 1-2, 5-6, 9, 11, 17-18, 24-26 and 28 pursuant to 35 U.S.C. §102(b) is respectfully requested at this time.

Rejection of Claims 1-2, 5 and 26 Under 35 U.S.C. §102(b)

The Examiner has rejected claims 1-2, 5 and 26 under 35 U.S.C. 102(b) as being anticipated by Steffens et al. (U.S. Patent 5,681,721; Steffens). The Examiner contends that Steffens teaches a thrombolytic composition comprising an effective amount of urokinase

comprising the polypeptide set forth in SEQ ID NO:83 and that residues 2-89 of Steffens SEQ ID NO:2 is identical to residues 1-88 of SEQ ID NO:1 of the current application. The Examiner further contends that Steffens teaches a composition comprising the uPA connecting peptide and protease domain (residues 90-365 of SEQ ID NO:83) which is 100% identical to residues 1-276 of SEQ ID NO:5 of the present application (the Examiner stated SEQ ID NO:1, but Applicants presume that the Examiner intended to write SEQ ID NO:5, as it is the only sequence listed in claim 5). The Examiner has further rejected claim 26 as being anticipated by Steffens because, in the Examiner's view, Steffens teaches a pharmaceutical composition comprising polypeptides.

Applicants are unable to understand the Examiner's rejection. SEQ ID NO:2 consists of 12 amino acids, so it is impossible for residues 2-89 of SEQ ID NO:2 to even exist, let alone anticipate the present invention. However, assuming that the Examiner meant to cite residues 2-89 of SEQ ID NO:83 against Applicants' SEQ ID NO:1, this does not anticipate the present invention because claim 1 as amended recites a composition comprising a uPA kringle that consists of a polypeptide having the amino acid sequence corresponding to SEQ ID NO:1. Steffens teaches a composition that does not consist of the sequence set forth in claim 1, but rather a much longer sequence that is not identical to that set forth in the present claim 1, and therefore is not anticipated.

The Examiner also rejects claim 5 as being anticipated because, in the Examiner's view, Steffens teaches a composition (residues 90-365 of SEQ ID NO:83) that is 100% identical to SEQ ID NO:5 in Applicant's claim 5. Applicants submit that claim 5 as presently amended recites a composition comprising the connecting peptide and protease domains of uPA that consists of a polypeptide having the amino acid sequence corresponding to SEQ ID NO:5. Steffens teaches a composition that does not consist of the sequence set forth in claim 5, but rather a much longer sequence that is not identical to that set forth in the present claim 5, and therefore is not anticipated.

The Examiner rejection of claim 26 also does not stand. Applicants, as set forth above, submit that Steffens does not teach any of the polypeptides or compositions presently claimed but rather teaches a completely different and non-identical polypeptide, and thus, the cannot anticipate the present invention.

For the reasons set forth above, Applicants submit that the rejection of claims 1-2, 5 and 26 have been overcome and the rejection pursuant to 35 U.S.C. §102(b) should be

reconsidered and withdrawn.

Rejection of Claims 1-2, 5-6, 9, 11, 17-18, 24-26, 28 and 54-55 Under 35 U.S.C. §103(b)

The Examiner has rejected claims 1-2, 5-6, 9, 11, 17-18, 24-26, 28 and 54-55 pursuant to 35 U.S.C. §103(b) as being obvious over Gurewich taken with Li et al. and Flora et al (U.S. Patent 4,761,406; Flora). The Examiner has restated his rejections in view of Gurewich, but admits that Gurewich does not teach a pharmaceutical composition or a kit comprising the composition comprising a polypeptide that comprises uPA kringle, uPA growth factor domain, and/or the connecting peptide. The Examiner cites Flora as teaching kits which facilitate strict compliance with methods of treatment and include a pharmaceutical composition, which is applied to claims 54 and 55. The Examiner concludes that it would have been prima facie obvious to one of ordinary skill in the art to formulate a composition comprising uPA kringle uPA growth factor domain, and/or the connecting peptide into a kit.

The three-prong test which must be met for a reference or a combination of references to establish a *prima facie* case of obviousness has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

None of these criteria have been met here.

As set forth above, Gurewich does not teach any of the compositions presently claimed, and Li et al. and Flora do not correct this defect. The skilled artisan would find no suggestion or motivation to combine Gurewich, which does not teach the instant compositions, with Li et al. which similarly fails to teach the instant compositions, with Flora, which teaches kits for the treatment of osteoporosis. Further, Gurewich teaches that thrombolytic therapies other than the fusion drug disclosed by Gurewich result in reocclusion within hours after

successful lysis of a thrombus (column 17, beginning at line 40), and therefore, there is no motivation to use the polypeptides of the present invention because they are regarded as ineffective. Further Gurewich teaches that urokinase polypeptides have a very short effective half life in the plasma and can only be administered intravenously, and thus can not be self administered (column 5, beginning at line 58 to column 6). Therefore, Gurewich teaches that a urokinase that is not a fusion drug consisting of amino acids 1-132 and a drug are ineffectual for their intended purpose, and provides no motivation to use the polypeptides of the present invention.

Gurewich similarly fails to offer any reasonable expectation of success in using the polypeptides and compositions of the present invention. As discussed above, Gurewich teaches that urokinase polypeptides have a short half life and do not lend themselves to self administration. Further, Gurewich fails to disclose that the fusion drug has any effect on modulating muscle contractility, and thus, the skilled artisan would have no reasonable expectation of success in using the presently claimed compositions to modulate muscle contractility. Therefore, the combined teachings of Gurewich, Li et al. and Flora are that the compositions presently claimed have a short half life, cannot be self administered, and have no effect on muscle contractility. This offers the skilled artisan no reasonable expectation of success, and therefore fails to meet the criteria necessary to render the present invention *prima facie* obvious.

For the reasons set forth above, Applicants submit that claims 1-2, 5-6, 9, 11, 17-18, 24-26, 28 and 54-55 are not obvious over Gurewich taken with Li et al. and Flora and the rejection of these claims pursuant to 35 U.S.C. §103(b) should be reconsidered and withdrawn.

Provisional Obviousness Type Double Patenting Rejection

The Examiner has provisionally rejected claims 1 and 26 as being in conflict with claim 3 of U.S. Application No. 09/968,752 (the '752 application) under the judicially created doctrine of double patenting. The Examiner contends that claim 3 of the '752 application claims a pharmaceutical composition comprising a UPK (*i.e.*, tcuPA) that comprises a sequence which reads on SEQ ID NO:1 of the present claim 1. The Examiner further argues that since claim 1 of the present application sets forth a composition without further specifying what the composition is, claim 3 is an obvious variation of claims 26.

The present claims are not obvious over claim 3 of the '752 application. The analysis used to assess an obvious-type double patenting is parallel to that used to analyze a 35 U.S.C. §103 rejection. *See* MPEP §804. Thus, there must be some suggestion or motivation either in the references themselves or in the knowledge generally available to those of skill in the art to modify the reference (the co-pending '752 application), there must be a reasonable expectation of success, and the reference (the co-pending '752 application) must teach or suggest all of the claim limitations.

Claim 3 of the '752 application recites a composition comprising tcuPA and suPAR. TcuPA is the two chain urokinase and suPAR is a soluble urokinase receptor. These are taught as a composition for stimulating fibrinolytic activity. Claim 1 of the present invention recites a composition comprising an isolated uPA kringle in an amount effective to modulate contractility of a mammalian muscle or endothelial cell or tissue wherein the uPA kringle consists of a polypeptide having SEQ ID NO:1. SEQ ID NO:1 is the kringle fragment of the uPA molecule and is 88 amino acids in length, whereas the tcuPA molecule is 411 amino acids in length. Therefore, these are substantially different molecules and the skilled artisan would find no motivation to arrive at the present invention given these divergent molecules. In addition, fibrinolysis is a substantially different process from modulation of muscle contractility, and the skilled artisan would find no motivation to treat strikingly different conditions with strikingly different compounds.

Moreover, there is no reasonable expectation of success in arriving at the present invention from the teachings of the '752 application. The '752 application teaches that scuPAR in combination with tcuPA is more effective at dissolving blood clots than either compound alone. There is no indication that the combination of tcuPA and scuPAR would result in the modulation of muscle contractility and the skilled artisan could not expect that a pharmaceutical composition comprising the kringle domain of uPA and a pharmaceutical composition comprising the entire tcuPA molecule as well as a soluble receptor for tcuPA to have similar functions. Thus, there is no reasonable expectation of success in arriving at the present invention, and the '752 application does not render the present invention obvious.

For the reasons set forth above, Applicants respectfully request reconsideration and withdrawal of the obviousness type double patenting rejection of claim 1 and 26

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 1-2, 5-9, 11-12, 14-18, 22, 24-26, 28 and 54-55 are now in condition for allowance. Applicants further submit that no new matter has been added by way of the present amendment. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

Douglas B. Cines, *et al.*

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(Date)

By: Kathryn Doyle

KATHRYN DOYLE, Ph.D, J.D.
Registration No. 36,317
MORGAN, LEWIS & BOCKIUS, LLP
1701 Market Street
Philadelphia, PA 19103-2921
Telephone: (215) 963-5000
Direct Dial: (215) 963-4723
Facsimile: (215) 963-5001
E-Mail: kdoyle@morganlewis.com
Attorney for Applicants

KD/JDGB